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# LYCOPENE AND ITS POTENTIAL NUTRITIONAL ROLE FOR PATIENTS WITH HEART FAILURE

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ABSTRACT OF DISSERTATION

Martha J Biddle

The Graduate School

University of Kentucky  
2011

LYCOPENE AND ITS POTENTIAL NUTRITIONAL ROLE FOR PATIENTS WITH HEART FAILURE

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ABSTRACT OF DISSERTATION

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A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy  
in College of Nursing at the University of Kentucky

By  
Martha J Biddle

Lexington, Kentucky

Chair: Dr. Debra Moser, Professor of Nursing

2011

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ABSTRACT OF DISSERTATION  
LYCOPENE AND ITS POTENTIAL NUTRITIONAL ROLE FOR PATIENTS WITH HEART FAILURE

Lycopene is an antioxidant found in natural and processed foods. The connection between antioxidants and heart disease has been explored in several observational studies<sup>1-4</sup>, yet very few investigators have examined the impact of dietary antioxidants in patients with advanced heart disease such as heart failure (HF). A novel strategy for preventing or delaying the complications of HF related to inflammation and oxidative stress may be to increase dietary lycopene.

The purpose of this dissertation was to test the impact of dietary intervention consisting of lycopene (V8® juice) on biomarkers of inflammation and oxidative stress in patients with HF; Prior to testing the dietary intervention, preliminary work was conducted: 1) a review of the literature on dietary lycopene interventions in patients with HF and 2) a longitudinal study to examine whether lycopene and sodium intake interact to produce an effect on event-free survival in patients with HF.

Forty patients with HF were randomly assigned to one of two treatment groups (intervention and usual care). The intervention group received 24 mg of lycopene by drinking 11.5 ounces of V8® 100% vegetable juice daily for 30 days. The usual care group continued their usual diet. Serum levels of uric acid and C-reactive protein were obtained to determine the impact of the lycopene dietary intervention. Patients in the intervention group had higher levels of plasma lycopene after one month drinking V8® juice. We also found a significant decrease in plasma CRP levels among women in the intervention group, while there was no change in CRP levels among men in the intervention group.

This dissertation has provided insight about lycopene as a potential nutritional intervention for patients with HF, aimed at reducing inflammation and oxidative stress. This dietary intervention is practical, easy to replicate, cost effective and is safe for patients with HF. Additional research is needed to determine the effects of long-term outcomes of dietary antioxidants in patients with HF.

Key Words: heart failure, inflammation, antioxidants, lycopene, oxidative status

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Student's Signature

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LYCOPENE AND ITS POTENTIAL NUTRITIONAL ROLE FOR PATIENTS WITH HEART FAILURE

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DISSERTATION

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## CHAPTER ONE

### Introduction

Heart failure (HF) is a growing concern for healthcare providers due to upward spiraling rates of rehospitalizations.<sup>5-7</sup> HF places a tremendous economic burden on our healthcare system with the cost of hospitalizations exceeding 39.2 billions for 2010.<sup>8</sup> HF has affected nearly 5.8 million patients in the US, with the American Heart Association (AHA) estimating 670,000 new cases will develop each year.<sup>9</sup> Heart failure is primarily a condition of the elderly, as the incidence of HF approaches 10 cases per 1000 in those over the age of 65.<sup>9 10</sup> This condition is responsible for 900,000 hospitalizations annually, more than for any other medical cause among the elderly.<sup>8</sup>

Nutrition could play an important role in the prevention and treatment of HF.<sup>11</sup> HF is a multisystem disorder in which systemic inflammation is a predominant process in the pathophysiology of HF. Inflammation is a potential target for nutrition therapy.<sup>12</sup> However, current evidence-based guidelines provide very little in the way of recommendations for the nutritional management of patients with HF.<sup>13, 14</sup> The reason for the lack of guideline recommendations related to nutrition is the limited amount of research in this area.

Certain foods have components that potentially could attenuate inflammatory processes by providing exogenous antioxidant sources to supplement the endogenous antioxidant defense system. Oxidative stress occurs when the endogenous antioxidant defense system is overwhelmed by reactive oxygen species (ROS).<sup>15, 16</sup> Reactive oxygen species are formed intracellularly during mitochondrial electron transport and cause damage to the myocardium.<sup>17-19</sup> The response to myocardial damage is activation of the inflammatory

process, which begins with endothelial secretion of chemotatic molecules and can lead to cardiac dysfunction, cardiac apoptosis and/or necrosis.<sup>18, 19</sup> Thus of particular nutritional interest is the antioxidant effect of certain bioactive food compounds that potentially reduce the inflammation process in HF.

There is abundant evidence that dietary patterns characterized by high intake of fruits and vegetables are associated with a lower risk of obesity, hypertension, diabetes, cancers, stroke and coronary heart disease, all of which have some degree of systemic inflammation implicated in their pathophysiology.<sup>20-25</sup> The mechanism by which fruits and vegetables reduce cardiovascular disease risk has not been defined clearly. A plausible explanation may be the antioxidants present in all fruits and vegetables.<sup>26</sup> The bioactivity of antioxidants may account for the cardioprotective benefit seen when fruits and vegetables are consumed in large amounts.

Antioxidants are biochemical nutrients found in foods that can prevent or slow the oxidative damage to the human body, enhance immune defense and lower the risk of inflammation.<sup>27-30</sup> Antioxidants are found abundantly in fruits and vegetables, as well as in other foods including nuts, grains, and some meats, poultry, and fish. Antioxidants exist in exogenous and endogenous forms.

Exogenous antioxidants must be obtained through the diet. The most common exogenous antioxidants are micronutrients like vitamin A, C and E, and phytochemicals such as flavonoids and carotenoids<sup>27</sup> ( see Table 1-1 for a glossary of terms). Endogenous antioxidants occur naturally in the body. The endogenous antioxidant defense system includes superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase(CAT)<sup>31</sup> Both forms of antioxidants

protect cells from the oxidative stress caused by unstable molecules known as free radicals.

Reactive oxygen species are a type of free radical.<sup>28, 30, 32</sup>

Free radicals are the natural by-products of normal cell processes. Free radicals are molecules with incomplete electron shells that make them more chemically reactive than those with complete electron shells.<sup>31</sup> Antioxidants neutralize free radicals by donating one of their own electrons, ending the electron-"stealing" reaction.<sup>30</sup> Despite donating an electron, antioxidants remain stable and don't become free radicals themselves. By reducing the negative consequences of oxidative stress, antioxidants prevent cell and tissue damage that can lead to disease.<sup>17, 30</sup> Under homeostatic conditions, there is balance between oxidative activities and intracellular levels of antioxidants and this balance is vital for the survival of organisms and health.<sup>30, 31, 33</sup> The disruption of this balance is thought to be the genesis of a multitude of diseases.<sup>31, 33</sup>

Lycopene is a naturally occurring antioxidant and a micronutrient with important health benefits. Lycopene exhibits antioxidant action by (1) exerting its strong affinity for singlet oxygen quenching, (2) protecting cells from lipid peroxidation and (3) enhancing cellular gap junction communication.<sup>34-37</sup> Lycopene may actually stimulate the endogenous enzymatic antioxidant system.<sup>34, 38</sup>

Tomatoes and tomato products are a major source of lycopene in the diet. Approximately 80% of the lycopene consumed in the U. S. comes from processed tomato products.<sup>39</sup> Tomatoes and tomato products are considered healthy as they are cholesterol free, low in calories and fat, good sources of vitamins A, C & E, as well as potassium and lycopene. A

diet rich in lycopene-rich food products may have potential health benefits for individuals with a high oxidative stress load.

The past decade has seen a number of improvements in treatment options for patients with HF, specifically in pharmacologic regimens. Researchers have gained a better understanding of the pathophysiology of the condition, but more is needed. Researchers and clinicians are now looking for less demanding treatment options for the patient with HF. As it stands, patients with HF must become expert self care clinicians to manage their condition on a daily basis. Treatment strategies that are easily adapted, low cost, without side effects, and can be part of a daily routine without intensive external monitoring are needed. Therefore this dissertation is centered on the research question “Can lycopene, as a potent antioxidant, found naturally and abundantly in fruits and vegetables, be used as a dietary intervention in patients with HF to reduce inflammation and improve outcomes?”

In chapter two of this dissertation, the results of a critical review of the literature related to antioxidant use in HF are presented. This review began as a broad investigation into lycopene as an antioxidant. The review then narrowed to focus on research studies using lycopene as a dietary intervention in HF. Lastly, the review focused specifically on studies in which patients with HF were enrolled as the sample population to test dietary interventions with lycopene.

In chapter three of this dissertation, the results of a study designed to determine whether higher intake of lycopene would be associated with better event free survival in patients with HF, independent of sodium content are presented. This was a longitudinal, prospective study of 212 patients with HF. Food diaries were kept by patients for four days. Diet



nutrient analysis was performed using Nutrition Data System Software™. Patients were grouped by the median split of lycopene level of 2471 mcg/day and stratified by daily sodium intake levels above and below 3 grams. Patients were followed for up to 3 years to collect data on HF hospitalization and cardiac mortality. Cox proportional hazard regression was used to compare differences in cardiac event-free survival between higher and lower lycopene intake groups within each stratum of sodium intake level. Lycopene intake above 2471 mcg/day was associated with longer cardiac event-free survival compared with lower lycopene intake after controlling for age, gender, HF etiology, body mass index, NYHA functional class, LVEF, and total comorbidity score ( $p = .003$ ). The worst cardiac event-free survival was observed in the low lycopene intake group regardless of sodium intake level.

In chapter four, results are presented from a randomized, controlled pilot study. This was a study conducted to determine the feasibility of a lycopene intervention in patients with HF, assessing for the impact of lycopene intake on biomarkers of inflammation and oxidative stress. Forty patients with HF (age  $66 \pm 10$ , 43% female) were randomized to either a usual care control group or a 30 day dietary intervention of daily lycopene intake. Patients randomized to the lycopene group consumed an 11.5 ounce can of V8® low-sodium vegetable juice once a day for 30 days. This 100% vegetable juice provided 24mg of lycopene. Serum samples of c-reactive protein (CRP), uric acid and b-type natriuretic peptide (BNP) were obtained pre and post intervention. Dietary intake was established with 4- randomly placed phone calls to collect 24-hour dietary recalls per patient over the 30 days. We used repeated measures ANOVA to test the impact of the intervention and controlled for disease severity using BNP as a surrogate measure.

Chapter five includes a summary and concluding remarks based on all the chapters. Recommendations for practice and future research are outlined.

## CHAPTER TWO

### Lycopene: A Critical Review of the Literature

#### **Introduction**

The purpose of this paper is to critically analyze the literature on the impact of dietary lycopene interventions on inflammation and oxidative stress in patients with HF. Research in the past two decades has found a strong link of the inflammatory response and oxidative stress with disease progression in HF<sup>12, 40-42</sup>, yet there is little research about non-drug interventions to address this problem.

#### Inflammation in HF

HF has an inflammatory component that is manifested in the following features: 1) reduced myocardial contractility; 2) left-ventricular dysfunction; 3) reduced cardiac index; and 4) endothelial dysfunction. There are currently three recognized pathways for inflammatory activation in HF: 1) direct antigenic stimulation, as is the case of a virus or bacteria infecting the myocardium; 2) activation secondary to cardiac injury such that the myocardium renders autoimmune type antigens capable of generating an inflammatory response against the heart; and 3) activation as a result of cytokine release by the cardiac cells, in response to hemodynamic stress on the vasculature or the cellular level of heart tissue<sup>42</sup>.

Specific serum biomarkers of inflammatory status in HF have been identified and include C-reactive protein (CRP). This biomarker has been studied extensively and has a strong association with HF disease severity<sup>40, 43-46</sup>. A basic understanding of the underlying mechanisms of inflammation, oxidative stress and the antioxidant defense system against a

permanent threat to myocardial cells is important to understanding why lycopene might be a potential intervention to reduce inflammation in HF.

#### Oxidative stress in HF

Oxidation is a normal consequence of cellular metabolism. Oxidative stress is an abnormal imbalance between the antioxidant system and the byproducts of oxidation. Free radicals are the result of oxidation, are potentially harmful, but are usually checked by the antioxidant system. Free radicals are connected with the development of diseases such as cancer, diabetes, infections, cardiovascular disease and also are thought to play a role in the aging process<sup>40</sup>. The regulation of oxidation is vital for maintenance of cellular homeostasis, however conditions of excess free radical production (oxidative stress) result in cell damage, frequently leading to cell and tissue dysfunction and ultimately to conditions such as HF<sup>47-49</sup>. In a study by White et al., patients with worsening HF and with a mean ejection fraction (EF) of 23% had evidence of significantly higher levels of biomarkers of oxidative stress and inflammation when compared to age-matched controls<sup>50</sup>.

To better understand oxidative stress, a review of the cellular components involved is important. Mitochondria are considered to be the main cellular source of reactive oxygen species (ROS; i.e., molecules that result from oxidation) during homeostasis<sup>49</sup>. Free radicals are inherently unstable by virtue of their single unpaired electron, thus tending to be highly reactive and transient. When free radicals come into contact with oxygen, a single electron is paired and the result is superoxide radical anion<sup>47, 49</sup>. Superoxide radical anion is considered to be the starter radical from which all other oxygen radicals are derived. Superoxide anion can act as both an oxidant and a reductant, depending on the environmental pH and the substrate with

which it reacts<sup>51</sup>. Superoxide radicals are rapidly converted to hydrogen peroxide, and further catalyzed by enzymes to a hydroxyl radical, which is the most potent oxidant in aerobic metabolism<sup>51</sup>. Minimal cellular damage is achieved when the response includes endogenous and exogenous interacting systems of antioxidant compounds, antioxidant enzymes and repair enzymes.

Oxidative stress results from increased exposure to oxidants or from decreased protection against oxidants, both of which may occur simultaneously, thus creating an imbalance<sup>51</sup>. The first level of response to oxidative stress is the antioxidant defense and repair system that minimizes the damage that naturally occurs in the presence of ROS<sup>52</sup>. Antioxidant compounds are sacrificed to oxidants in order to directly protect more important cellular components. Antioxidants have a variety of chemical structures and are either water-soluble or fat-soluble. Antioxidants are either synthesized in the body (endogenous) or consumed in the diet (exogenous). Examples of endogenous antioxidants include uric acid, coenzyme Q, lipoic acid, and some steroid hormones such as estrogens. Dietary antioxidants include vitamins C, E, carotenoids, and phenolic compounds.

### Lycopene

This paper focuses on lycopene as a dietary antioxidant. Lycopene is the most predominant carotenoid in human plasma. Lycopene is a carotenoid found naturally in plant sources and has a chemical structure with 11 linearly arranged conjugated double bonds and 2 non-conjugated double bonds<sup>53</sup>. Because of the high number of conjugated double bonds, lycopene is considered one of the most potent antioxidants due to its singlet oxygen-quenching ability<sup>19, 37</sup>.

More than 600 carotenoids have been discovered and share a common structural feature, such as a polyisoprenoid structure and conjugated double bonds<sup>53</sup>. The chemical structure of carotenoids is a key determinant of the physical property, chemical reactivity and biologic function observed<sup>36</sup>. Carotenoids are strongly influenced by other molecules in the environment, particularly proteins and lipids. The unique structure and combination of carotenoids may influence the bioavailability, absorption, circulation and distribution of lycopene in tissues<sup>37 36, 53</sup>. Carotenoids are natural pigments synthesized by plants and microorganisms<sup>37</sup>. The majority of carotenoids, including lycopene, are without vitamin A activity. The interest in lycopene has grown recently due to studies that have suggested a role in human health and disease<sup>34, 54</sup>.

More than 80% of lycopene consumed in the United States is from tomatoes and tomato products<sup>54</sup>. The primary sources for lycopene in the diet are spaghetti/pasta sauce, ketchup, salsa, tomato soup, canned tomatoes, raw tomatoes, tomato sauce, tomato paste, vegetable juice cocktail, and watermelon<sup>39</sup>. Other fruits such as apricots, guava, papaya and pink grapefruit also contribute lycopene to the diet. Lycopene concentration varies as a result of the color and type of tomato. Some deep red varieties contain 50mg per 100 grams of raw material (about the size of one medium tomato), while yellow varieties contain 5mg/100 grams (100 grams = 3.5 ounces)<sup>39, 54</sup>. Lycopene has varied bioavailability and has tissue specific distribution related to its lipophilic nature; both of these characteristics are important in the role of an antioxidant<sup>39</sup>.

#### Bioavailability of Lycopene

Many factors can influence the bioavailability of lycopene, such as the food matrix containing the lycopene, the absorption rate of the stomach and the co-ingestion of fat as a delivery medium<sup>37</sup>. Thermal processing such as cooking with heat causes a disruption of the chemical structure of lycopene and enhances bioavailability<sup>55, 56</sup>. The improved bioavailability of lycopene from processed foods has also been attributed to its release from the ruptured plant cells during mechanical processing (grinding, pulverizing) and due to heat induced *trans*- to *cis*-isomerization<sup>57</sup>.

The absorption rate in the stomach and duodenum also affects the bioavailability of lycopene. The action of bile salts and pancreatic lipases assist in the digestion process. Lipids play an important role in lycopene dissolution and absorption. Lipid droplets containing the lycopene enter the duodenum and transfer into the mucosal cells via passive diffusion<sup>19, 39, 58</sup>. Chylomicrons carry lycopene from the intestinal mucosa to the blood stream via the lymphatics<sup>39, 58</sup>. Lycopene is transported in the plasma by lipoproteins, and is concentrated in the hydrophobic core of the lipoprotein particle<sup>39</sup>. Experimental studies have been conducted that suggest it is important to consider bioavailability and food product choice in designing interventions with lycopene.<sup>55, 56, 59-61</sup>

### Lycopene Interventions in Healthy Individuals

Experimental studies of dietary lycopene in healthy adult subjects have been used to test the impact of lycopene on a number of variables. Two common themes are evident in these intervention studies (See Table 2-1). First, when an increased amount of dietary lycopene is consumed there is a corresponding increase in the plasma level of lycopene<sup>60, 61</sup>. Second, findings from these studies indicate an increased amount of dietary intake of lycopene

consistently decreases biomarkers of inflammation (CRP levels) and biomarkers of oxidative stress (lipid peroxidation)<sup>57, 60, 62-64</sup>. As well, several small studies have demonstrated the variations of the bioavailability of lycopene, specifically in different food sources and when delivered in different mediums (canned vs. raw, paste vs. juice, olive oil vs. sunflower oil)<sup>65, 66</sup>.

Investigators have tested lycopene bioavailability and absorption rates and studied a variety of food products containing lycopene, but only in very small sample sizes.<sup>60, 61, 66-68</sup> For example, the investigators in one intervention study tested 11 healthy individuals to determine whether consumption of diced tomatoes cooked with olive oil resulted in higher plasma lycopene concentrations than consumption of diced tomatoes cooked without olive oil<sup>67</sup>. Plasma lycopene concentrations were measured after 5 days of a lycopene washout period and again after a five-day dietary intervention. The investigators concluded that the addition of olive oil to tomatoes greatly increased the absorption of lycopene as demonstrated by an 82% increase in plasma trans-lycopene ( $P = < 0.001$ ) and a 40% increase in cis-lycopene ( $P = 0.002$ ) concentrations<sup>67</sup>. A smaller intervention study conducted in Northern Ireland with 6 healthy individuals tested two types of cooking oil with lycopene containing food products (tomato soup and canned tomatoes)<sup>68</sup>. The consumption of tomato products with olive oil significantly raised the plasma antioxidant activity from  $930 \pm 150$  to  $1118 \pm 184$  mmol/l, ( $p = .01$ ) but no effect was observed when the sunflower oil was used<sup>68</sup>. This investigation suggests the composition of oil used for cooking tomato products may affect the antioxidant activity and bioavailability of lycopene.

Healthy individuals ( $n = 60$ ; 30 men/30 women) who consumed a lycopene-free diet for 1 week were randomized to receive lycopene from eating Campbell's Condensed Tomato Soup ,



Campbell's Ready To Serve Tomato Soup or V8 Vegetable Juice, respectively, for 15 days<sup>60</sup>. After the intervention period, total lycopene concentrations significantly increased for those consuming condensed soup, ready to eat soup and V8 [by  $0.784 \pm 0.083$  (123% increase,  $P < 0.0001$ ),  $0.545 \pm 0.061$  (57%,  $P < 0.01$ ) and  $0.569 \pm 0.061$  (112%,  $P < 0.0001$ ) micro mol/Liter] when compared to baseline levels, respectively<sup>60</sup>. This study demonstrates that serum lycopene concentration changes as a result of intake of a variety of food products<sup>60</sup>. Collectively, these small intervention studies provide evidence to support the following when designing future experimental studies: 1) the anti-inflammatory effect of lycopene; and 2) the importance of considering bioavailability, food source and delivery medium when using dietary sources of lycopene.

#### Epidemiologic Studies of Lycopene

Several large epidemiologic studies have been conducted. The combined evidence from these studies suggests an inverse relationship between serum carotenoids in general and lycopene specifically and cardiovascular disease risk<sup>69-73</sup>. In a large prospective, longitudinal study of US male physicians, an association was found between increased vegetable intake and lower risk of coronary heart disease, independent of other cardiac risk factors<sup>74</sup>. Investigators were able to detect a 25% risk reduction even at the low end of vegetable consumption (1-2 servings per day). Similar findings from Ness et.al<sup>23</sup> and Law et.al<sup>75</sup> lend support to the findings in the Physician Health study. Cross sectional data from the National Health and Nutritional Survey III (NHANES) 1988-1994 demonstrated an association between levels of five carotenoids (lycopene included) and inflammation measured by CRP<sup>76</sup>. The NHANES data were from a large sample ( $n = 4557$ ) of young (mean age =  $38.6 \pm 8.6$ ) healthy individuals. While these studies do

not specifically identify lycopene as a micronutrient of interest, nor do they specify HF as a condition, there is enough evidence from these studies to provide a foundation for additional inquiry related to the purpose of this paper.

## **Methods**

The purpose of this paper was to examine the evidence about the impact of lycopene dietary interventions in patients with HF. A search of Pub Med, CINAHL, and the Cochrane Library was performed using the search terms 'lycopene', 'antioxidants', 'heart disease', 'heart failure', 'oxidative stress', and 'inflammation.' The search was limited to the time period between the years of 2000-2010 and to articles written in English. The following were inclusion criteria: 1) research reports; 2) human studies; 3) observational studies of dietary lycopene intake in patients with HF; 4) intervention studies of lycopene; and 5) dietary intake of food products containing lycopene, not supplements. Each manuscript was read and reviewed for content and applicability. The PubMed search resulted in the following results for each term used: (See Table 2-2)

- *lycopene* = 2682 articles
- *lycopene and heart disease* =104 articles
- *lycopene and inflammation* = 36 articles
- *lycopene and oxidative stress* = 304 articles
- *antioxidants and HF* = 2371 articles
- *lycopene and HF* =3 articles

## Results

There were no intervention studies of dietary lycopene intake in patients with HF. Only two studies have been conducted that lend support for the potential role of dietary lycopene in patients with HF to reduce inflammation as evidenced by measurement of biomarkers of oxidative stress.<sup>77, 78</sup>

A case-control evaluation of patients with HF moderate (class II) and severe (class III) HF according to NYHA classification (13 females, 17 males,  $73.8 \pm 7.4$  years old;  $n = 30$ ) were compared to age-matched controls (25 females, 30 males,  $76.3 \pm 8.5$  years old;  $n = 55$ ).<sup>77</sup> Investigators measured a circulating biomarker of oxidative stress (malondialdehyde-MDA) and plasma antioxidants (Vitamin A, E and carotenoids) levels. Significantly higher levels of oxidative stress and lower levels of plasma antioxidants were found in HF patients in comparison to controls. Levels of oxidative stress were found to be higher in New York Heart Association (NYHA) class III than in NYHA class II HF patients ( $p = .0012$ )<sup>77</sup>. The conclusion from this particular investigation indicates an association exists between increased oxidative stress and the general class of antioxidant carotenoids in patients with HF.

In a similar cross-sectional analysis (perhaps the same) by the Polidori et.al<sup>78</sup>, patients with moderate (class II) and severe (class III) HF according to NYHA classification, (14 male, 16 female,  $73.1 \pm 7.4$  years;  $n = 30$ ) were compared to age-gender matched controls (18 male, 12 female,  $80.0 \pm 17.4$  years;  $n = 30$ )<sup>78</sup> and were found to have significantly higher levels of plasma F8, 12-isoprostanes. Isoprostanes are sensitive and specific markers of lipid peroxidation. Levels of 8, 12-isoprostane F(2 $\alpha$ )-VI were significantly higher in class III than in class II NYHA HF

patients. The investigators also found the EF of HF patients to be inversely correlated to isoprotane levels and directly correlated to plasma levels of lycopene.

These two studies, conducted by the same investigator, which had small sample sizes, did find significant associations between plasma lycopene, biomarkers of oxidative stress and the data do provide insight into the potential role of dietary lycopene to manage oxidative stress in patients with HF.

### Critique

In these small studies, investigators observed an association between HF patients and two types of biomarkers of oxidative stress. The age of the patients in these studies is representative of other HF samples. The sample would have been more inclusive if class I and class IV NYHA patients were included in the analysis, as I-IV is representative of the complete trajectory of HF disease status. Multiple drug therapies such as ACE inhibitors, beta blockers and diuretics were considered in only one of the studies; this is of importance as many of these drugs are considered to have antioxidant properties and could have confounded the results when considered as a co-variate in the analysis. No differences were observed in these two studies between HF patients with an ischemic or non-ischemic etiology. The investigators excluded patients if they were smokers; this information would have added to the analysis as smoking history appears to have an association with antioxidant status.<sup>79, 80</sup>

The observation of a significant association between EF of HF patients and plasma levels of lycopene is of potential interest and warrants further studies in this area.

## **Discussion**

After completing this review of the literature, it is interesting to note that further research has not been conducted and makes me wonder why this has not occurred. My conjecture for the reason why research has not advanced in this area is because “nutrition interventions” are not deemed as important as pharmacological interventions; there is not the same level of funding available for nutritional interventions as there is available for pharmacologic interventions. Specifically, I believe that medical practitioners are more interested in providing drugs to patients than they are in taking the time to explain the importance of nutrition and how patients with HF can make simple changes in lifestyle related to nutrition. This conjecture is not evidence based, but is the experience of an advanced practice nurse with 20 years experience in caring for HF patients. The science of advancing treatment strategies for HF patients is primarily focused on pharmacologic interventions. The money for research is primarily available in pharmacologic studies. Hence, nutritional interventions appear to be designated to those individuals who have an interest in providing more than just pharmacologic treatment options to patients with HF.

## **Conclusion**

In conclusion, there is sufficient evidence to support the following regarding lycopene and HF: 1) HF is a condition of increased inflammatory response; 2) oxidative stress poses an independent threat at the cellular level and contributes to the inflammatory response; 3) there are endogenous and exogenous antioxidant defense systems that can reduce the level of inflammation and oxidative stress; 4) lycopene is a potent antioxidant that is associated with reduced biomarkers of lipid peroxidation and oxidative stress. For the reasons elucidated, there

has been no research on the impact of dietary lycopene intake on inflammation in HF. Yet, given the safety of dietary lycopene intake and based on the known scientific foundation, it is plausible to begin scientific inquiry into the potential role of lycopene in reducing inflammation and oxidative stress in patients with advanced cardiovascular disease such as HF. This process of scientific inquiry will help to elucidate whether increased dietary intake of lycopene has a cardioprotective role in HF specific to inflammatory and oxidative stress components in the pathophysiologic process.

## CHAPTER THREE

### Higher Dietary Lycopene Intake is Associated with Longer Cardiac Event-Free Survival in Patients with Heart Failure

#### Introduction

Heart failure (HF) remains a major cause of early death and is associated with high morbidity resulting in significant personal, societal and economic burden.<sup>82</sup> Hospitalizations account for the majority of expenses incurred in the care of patients with HF. Rates of HF hospitalizations have increased by approximately 200% over the past decade.<sup>83</sup> Additional strategies for managing HF are needed to reduce the personal and economic costs of HF.

Recent evidence suggests that nutrition may play a role in improving outcomes in patients with HF.<sup>13, 84-86</sup> Findings point to specific macro and micronutrients that may slow the trajectory of HF by decreasing the inflammatory process associated with HF, and reducing the amount of oxidative stress.<sup>13, 48, 87, 88</sup> Antioxidants such as lycopene, selenium and vitamin D may be targets for nutritional therapy. Lycopene in particular may be beneficial in HF due to potential cardioprotective effects. Numerous investigations in humans and animal models have demonstrated an inverse relationship between serum lycopene levels and risk of cardiovascular disease (CVD)<sup>62, 89-91</sup>.

The major source of dietary lycopene in the United States is fresh and processed fruits and vegetables, particularly tomatoes. Heat during processing alters the molecular structure of lycopene making it more bioavailable to human tissue<sup>39, 62, 92</sup>. Unfortunately, processed foods containing high levels of lycopene also contain high levels of sodium. Research investigating the potential benefits of lycopene must also consider the sodium content of such foods<sup>93, 94</sup>.

Therefore the purpose of this study was to determine the association between lycopene intake and cardiac event-free survival in patients with HF stratified by sodium intake levels.

## **Methods**

### Study Design

This was a longitudinal prospective study in which levels of dietary lycopene and sodium intake were measured at baseline. This study was part of a larger study titled “BMI, Nutrition, Inflammation, and Heart Failure Outcomes” (PI- Terry A. Lennie, R01NR 009280). Patients were followed for up to three years. Rehospitalizations and cardiac mortality data were obtained to examine the relationship between dietary lycopene intake and cardiac event-free survival after stratifying patients by sodium intake levels.

### Sample and setting

Patients were recruited from outpatient HF clinics associated with academic health centers in Kentucky, Indiana and Georgia. Patients were included if they had a diagnosis of chronic HF confirmed by a cardiologist and were on a stable medication regimen for at least 3 months. Patients were excluded if they had a history of acute myocardial infarction or cerebrovascular attack within the previous 6 months, were cognitively impaired, and had a co-morbid terminal illness or an inflammatory condition that suppressed appetite or required dietary restrictions other than sodium. A total of 246 patients were invited to participate. Six patients declined, 7 patients withdrew, 5 patients were lost to follow-up and 16 provided incomplete food diaries resulting in a final sample size of 212 patients.

## **Measurement of variables**

### Dietary lycopene and sodium intake



Dietary intake was measured by four day food diaries that included three weekdays and one weekend day. Food diaries were analyzed using the Nutrition Data System for Research (NDSR; Nutrition Coordinating Center, Minneapolis, MN)<sup>95</sup>. The analysis provided four day averages of patient's intake with data on 156 individual nutrients including lycopene and sodium.

#### Event-free survival

The primary outcome of this study was event-free survival. This is defined as the composite end point of time to first HF hospitalization (emergency department or inpatient admission with a primary diagnosis of HF) or a cardiac related death during the follow-up period. Data on hospitalization events or death were collected from patients/ family member interviews, medical record review, hospital administrative records and death certificates. A clinical expert on the research team reviewed all the data on reasons for hospitalization to ensure accurate categorization. Because of the possibility that a patient was admitted to various hospitals, patients/families were interviewed to obtain self-reports of admissions, which were then used to validate or augment electronic medical record data.

#### Covariates

Covariates included New York Heart Association (NYHA) functional classification, age, gender, body mass index (BMI) left ventricular ejection fraction (LVEF) and prescribed medications (i.e., ACE inhibitors, beta-blockers, angiotensin II receptor blockers, digoxin and diuretics). Total co-morbidity score was obtained using the Charlson Co-Morbidity Index<sup>96, 97</sup>.

## Procedure

The study received approval from the Institutional Review Board at each enrollment site. Patients with HF were referred to the study by cardiologists and nurse practitioners. All patients gave written informed consent prior to participating. Demographic and clinical characteristics were collected at baseline. Patients were visited in their homes by a trained research nurse who provided detailed oral and written instructions for recording all food and beverages consumed during the four day food diary collection. Digital scales were provided to measure the weight of each food. Food models were also provided for patients to estimate serving sizes when they found that weighing food was impractical (e.g., when eating at a restaurant). Patients were asked to provide a return demonstration of food diary recording and food measurement as a review of the procedure. Patients were also telephoned on the first day of the food diary recording to answer any questions they may have had. The morning after completion of the food diary, the patient met with the dietitian who reviewed the completed food diary. This process was to verify the serving sizes, obtain any missing information, and clarify food preparation techniques. These review sessions typically lasted 30-45 minutes. Lycopene and sodium levels were then determined using the NDSR software program for nutrient analysis. Lycopene and sodium daily consumption levels were totaled and then averaged over the four days of record keeping.

## Statistical Analysis

Data were analyzed using SPSS for Windows 17.0. Patients were dichotomized based on the median value for lycopene intake and the two groups were further stratified by the cut-point of 3 grams of sodium intake. For the purpose of data analysis, patients with a lycopene

intake less than median were defined as *low lycopene group* and those with an intake of greater than median split were defined as the *high lycopene group*. Independent *t* tests or chi square tests were used to compare the differences of sample characteristics between lycopene groups. Cox proportional hazard regression was used to compare the differences in cardiac event-free survival of patients in the lycopene groups stratified by sodium intake while controlling for age, gender, HF etiology, BMI, NYHA classification, LVEF and total co-morbidity burden. The proportional hazard assumption was confirmed through visual inspection of the log (-log) survival curves.

## **Results**

### Patient characteristics

Patient characteristics of the total sample and of the high and low lycopene intake groups are shown in Table 3-1. The average age of patients enrolled in this study was 60 years  $\pm 12$  (range 23-97 years). Sixty-eight percent of the patients were Caucasian and 29 % were African-American. Almost one-third of patients had preserved systolic function with LVEF > 40%. The common co-morbidities were hypertension and diabetes mellitus. The mean four day average intake of lycopene was 4091 mcg/day  $\pm$  4940 (range from 0 - 31,529) and the median was 2471 (25<sup>th</sup> percentile = 915, 75<sup>th</sup> percentile = 5076) mcg/day. Fifty one percent of patients had daily sodium intake greater than 3 grams per day. The average sodium intake of the high lycopene group was greater than the low lycopene group (Table 1). The majority of patients in both lycopene groups were classified as NYHA functional classification of II or III, and were on appropriate HF medication regimens of ACE inhibitors, diuretics and beta blockers.

### Cardiac events

During the follow-up period there were a total of 2 patients who died (1.0%) and 41 patients (19.3%) who were hospitalized with a primary diagnosis of HF or experienced a cardiac related death.

Using Cox hazard regression modeling, patients with a dietary lycopene intake above the median had longer event-free survival than those with a dietary lycopene intake below the median after multivariate adjustment. In the stratum of patients with sodium intake levels above 3 grams per day, the low lycopene group demonstrated 3 times greater risk of having a cardiac event compared to patients in the high lycopene group (Table 2). Adjusted survival curves for high versus low lycopene groups with each stratum of sodium intake are depicted in Figure 1A and 1B. Higher intake of lycopene was associated with longer event-free survival in both strata of sodium intake. In the stratum of patients with sodium intake less than 3 grams per day, low lycopene intake presented a 3.3 times greater risk of cardiac events when compared to the high lycopene group.

## **Discussion**

This is the first study to demonstrate that higher intake of lycopene independently predicted longer cardiac event-free survival regardless of sodium intake in patients with heart failure. These findings are important because they suggest a fruitful avenue for future research that some have been reluctant to follow due to the high sodium content of many tomato-based foods. Our findings suggest that the antioxidant properties of dietary lycopene may be more important to the health of patients with health failure than reducing sodium intake alone.

Our findings about lycopene are consistent with those of prior researchers who have reported inverse relationships between lycopene and the development of cardiovascular

disease (CVD)<sup>98</sup>. The previous evidence in support of the role of lycopene in the prevention of CVD comes primarily from observational studies on normal and at risk populations.<sup>3, 19, 62, 89, 91,</sup>

99-101

For example, in The Rotterdam Study, using a case-control design, investigators assessed the presence of calcified plaques in the abdominal aorta as a clinical indication of atherosclerosis<sup>4</sup>. The study sample consisted of 108 individuals with moderate to severe atherosclerosis compared to 108 age-gender matched controls without atherosclerosis. The investigators reported an inverse relationship between serum levels of lycopene and the presence of atherosclerosis when using a logistic regression model with multivariate adjustment<sup>4</sup>. The odds ratio for the highest compared to the lowest quartile of serum lycopene was 0.55 (95% CI, 0.25-1.22)<sup>4</sup>.

The strongest population based evidence for lycopene comes from a multi-center case control study (EURAMIC) that evaluated the relationship between adipose tissue antioxidant status and acute myocardial infarction.<sup>70</sup> Needle aspiration biopsy samples of the adipose tissue were taken after a myocardial infarction and levels of alpha carotene, beta carotene, lycopene and tocopherol were measured. Only lycopene was found to be protective with an odds ratio of 0.52 for the comparison of the 10<sup>th</sup> and 90<sup>th</sup> percentiles (95% CI, 0.33-0.82; p = 0.005).<sup>70</sup> A dose-response was also observed between each quintile of adipose tissue lycopene and the risk of myocardial infarction. The protective potential of lycopene was at the highest among individuals with the highest polyunsaturated fat stores<sup>70</sup>.

Evidence about the effectiveness of lycopene in heart disease has recently been extended to patients with HF. In a series of observational studies, Polidori et al. evaluated

plasma levels of malondialdehyde (MDA) and F2 isoprostane as biomarkers of oxidative stress and antioxidants levels (vitamin A, vitamin E, lutein, zeaxanthin and lycopene) in 30 HF patients with NYHA Class II and III compared to 30 age-gender matched controls (18 male, 12 female,  $80.0 \pm 17.4$  years)<sup>77, 78</sup>. Class II NYHA patients with HF had significantly lower levels of markers of oxidative stress (MDA and F2 isoprostane levels) and significantly higher levels of antioxidant intake (vitamin A, vitamin E, lutein, and lycopene) than NYHA III patients. Ejection fraction was inversely correlated with MDA levels in HF patients when compared to the controls. A positive correlation was found between plasma levels of lycopene, lutein and Vitamin A and ejection fraction, thus suggesting increased hemodynamic function of the heart in the presence of dietary antioxidants. These findings further suggest that antioxidants are depleted in patients with worse HF which may be linked to increased oxidative stress or perhaps as a result of lifestyle, disease or age-related reasons that can facilitate oxidative stress<sup>77, 78</sup>.

In a retrospective analysis of subjects enrolled in the Third National Health and Nutrition Examination Survey, Wood and Johnson reported a relationship was found between tomato consumption, serum lycopene levels and HF risk in individuals with periodontitis<sup>102</sup>. This dose-response relationship existed after adjusting for demographic, medical and lifestyle factors ( $p = 0.05$ ). When data were further adjusted for serum lycopene levels, the relationship between tomato consumption and HF risk in periodontally involved individuals remained high ( $p = < .05$ )<sup>102</sup>.

Approximately 80% of the sodium in the average American diet comes from processed foods and for the past two decades the average daily sodium intake among adults was greater than 3200mg<sup>103</sup>. Dietary sodium indiscretion is considered to be a precipitant in >20% of

patients hospitalized for decompensated HF and high sodium intake is an independent risk factor for HF exacerbation<sup>104-106</sup>. Because the richest sources of lycopene (processed tomato-based products such as ketchup, tomato juice, and pizza and spaghetti sauces) are also some of the highest in sodium, clinicians commonly have patients with HF avoid these foods. Our data suggest that foods containing high levels of lycopene may be beneficial regardless of their sodium content.

A potential limitation of this study was the use of self-recorded food diaries. We used a combination of strategies to increase the accuracy of the food diaries. Our participants were given detailed instructions for the diary by an experienced HF research nurse. In addition to the verbal instruction, written and graphic materials were provided to each participant. Patients also were given digital food scales to assist with measurement of food portions. Food models were utilized to help with estimation of serving sizes. Food diaries were reviewed with the patient by a dietitian. Further motivation to accurately complete the food diary was enhanced by providing a nutritional analysis report to the patient. Another limitation to this study is that we did not obtain a direct measurement of oxidative stress or inflammation and therefore we cannot conclude the potential mechanism responsible for our findings.

Our findings do support the potential cardioprotective benefit of higher lycopene intake in the presence of increased sodium levels in food products consumed by patients with HF. Increased sodium intake in patients with HF is associated with an increase in fluid retention that is often responsible for the exacerbation of HF symptoms. However, the potentially detrimental effect of increased sodium content in processed food products may not overshadow the benefit of lycopene in HF patients. However, further studies are needed to clearly delineate the

interaction of lycopene and sodium in patients with HF, and the results from our study should not be interpreted as suggesting that sodium restriction is unnecessary in patients with HF, even in the presence of high lycopene intake.

## **Conclusion**

Future research should include use of randomized control trials of various levels of dietary lycopene intake in HF patients stratified by their usual sodium intake. A diet with a high lycopene intake has the potential to improve cardiac event free survival outcomes in HF patients. The study of dietary factors that lead to a diet rich in antioxidants is essential for optimization of interventions aimed at reducing the burden of HF. Additional research should be conducted to examine the potential impact of lycopene from a variety of food products on the inflammatory process in patients with HF.



## CHAPTER FOUR

### Lycopene Dietary Intervention: A Pilot Study in Patients with Heart Failure

#### Introduction

Heart failure (HF) is recognized as a significant contributor to cardiovascular mortality and morbidity rates in North America and most Western civilizations and is considered one of the most problematic threats to healthcare. HF is commonly a result of ischemic heart disease or hypertension. Despite advances in the treatment of HF, the mortality and hospitalization rates for HF continue to rise with a 45% re-hospitalization rate at 6 months and a 27% re-hospitalization rate at 90 days.<sup>107, 108</sup> Over 800,000 hospitalization visits are reported annually by Medicare and these visits consume the majority of healthcare dollars required to care for patients with HF.<sup>109</sup>

The connection between increased antioxidant intake and reduced cardiovascular disease (CVD) risk has been demonstrated in several epidemiologic and observational studies.<sup>1-4</sup> Although HF has a major inflammatory component and ischemic cardiovascular disease is the most common cause of HF, few investigators have examined the potential impact of increased antioxidant intake in improving outcomes in HF patients.

There is substantial evidence to indicate that antioxidants play a role in reducing the inflammatory and oxidative stress processes that are thought to be responsible for atherosclerosis in CVD.<sup>110-112</sup> Lycopene is a superior antioxidant found in natural and processed food products and is considered to be one of the most efficient at reducing free radicals.<sup>89, 113</sup> Given the role of inflammation in HF, a novel strategy for preventing or delaying the

complications of HF may be to increase lycopene intake in the diet. Thus, the purpose of this randomized, controlled pilot study was to test the effect of an intervention consisting of intake of a food product concentrated with lycopene (V8® juice) on biomarkers of inflammation and oxidative stress in patients with HF.

***Specific Aim #1:*** Compare the impact on serum levels of uric acid and C-reactive protein (CRP) in a group of patients with HF in the intervention group who consume 11 ounces of V8® juice daily to levels in a control group of HF patients who did not consume V8® juice daily controlling for HF severity as reflected by b-type natriuretic peptide (BNP).

***Hypothesis #1:*** Compared to a control group and to their own baseline, HF patients randomized to consume 11 ounces of V8® juice daily for one month will have lower levels of uric acid and CRP regardless of BNP level.

***Specific Aim #2:*** To test adherence to the intervention by comparing plasma levels of lycopene in the intervention versus control groups.

***Hypothesis #2:*** Compared to a control group and to their own baseline, HF patients randomized to consume 11 ounces of V8® juice daily will have higher levels of plasma lycopene after one month of intervention.

***Specific Aim #3:*** To determine the impact of consumption of 11 ounces of V8® juice daily on sodium intake.

## **Methods**

### **Study Design**

This study was a two-group randomized controlled intervention trial in which patients were randomized to either an intervention group (n=22) or usual care/control group (n=18).

Patients were recruited from outpatient and inpatient healthcare settings in Central Kentucky. The intervention group was given one 11.5 ounce can of V8® 100% Low-Sodium Vegetable juice to drink each day for 30 days while consuming their normal habitual diet. The usual care group continued to consume their habitual diet. Data for both groups was collected at baseline and one month post intervention. Data collection included sociodemographic and clinical information, random 24 hour dietary food recalls, and blood samples for levels of uric acid, CRP, BNP and lycopene.

### Sample and Setting

Patients were recruited from a community hospital and an academic outpatient cardiology clinic in Central Kentucky. Eligibility criteria for patients in this study included: 1) confirmed diagnosis of HF, with preserved or non-preserved ejection fraction, 2) hospitalized for HF within the last 6 months; 3) able to read and write English; 4) living independently (i.e., not institutionalized). Patients were excluded from the study if they: 1) were younger than 21 years of age; 2) had end stage renal disease, a co-morbidity with a known inflammatory component, or a disease or illness that was predicted to cause death within the next 12 months; 3) had impaired cognition; or 4) disliked V8 juice. Forty three patients were invited to participate in the study. Three declined to participate due to time constraints. No patients withdrew or were lost to follow-up during the one month time frame. The final sample size was 40 patients. One baseline blood sample was dropped in the laboratory, therefore providing 39 baseline samples of lycopene and 40 post intervention samples of lycopene.

## Measurement

### Plasma Lycopene

Plasma lycopene was obtained from venous blood (approximately 5mL) that was drawn via needle and syringe from the lower forearm into EDTA vacutainer tubes (Fisher Scientific, Pittsburg, PA). Plasma was immediately separated from red blood cells by centrifuging at 1000 x g at 4°C for 10 min. Blood plasma was then placed into cryovials and stored at -80°C until high performance liquid chromatography (HPLC) analysis.

*Lycopene extraction:* Plasma (0.5mL) was mixed with 0.5mL ethanol containing 0.1% butylated hydroxytoluene and 2mL of HEAT (10 hexane/6 ethanol/7 acetone/7 toluene). The mixture was vortexed and then centrifuged for 5min at 300 x g. The upper non-polar layer was removed and the remaining aqueous plasma mixture was extracted twice more. The three non-polar extracts were combined and dried under nitrogen. The dried extract was stored at -80°C until HPLC-PDA analysis.

*Lycopene HPLC-PDA (photodiode array) analysis:* Samples were reconstituted in 1:1 200µL methanol/ Methyl *tert*-butyl ether (MTBE) and filtered through a nylon syringe filter. Samples were analyzed using an HPLC system (Waters 996) interfaced with a PDA detector (Waters 2996). Separation was achieved using a YMC C-30 column (Waters Corp., Milford, MA). A 30 min. gradient method employing methanol and MTBE was used with a flow rate of 1.3mL/min, column temperature = 30°C, and injection volume = 20 µL. Lycopene was quantified using an external calibration curve.

### C-Reactive Protein

C-reactive protein was measured using point-of-care methodology (Cholestech LDX Diagnostics, Inverness Medical Innovations). Venous blood (approximately 5mL) was withdrawn via a needle and syringe from the patient and placed into a purple top vacutainer. Serum was removed from the vacutainers using a pipette, 0.4ml was placed onto the Cholestech hsCRP cartridge, then placed into the Cholestech LDX<sup>®</sup> analyser. The Cholestech LDX<sup>®</sup> system uses reflectance photometry. This method of determining CRP levels has been demonstrated to provide reproducible, accurate and valid results.<sup>114</sup>

### Uric Acid

Uric acid was measured using standardized laboratory assay analysis at the University of Kentucky clinical laboratory. Venous blood (approximately 5ml) was withdrawn via a needle and syringe from the patient and placed into a green top vacutainer. Samples were refrigerated as necessary and taken to the clinical research laboratory for analysis using.

### B-type Natriuretic Peptide

B-type natriuretic peptide was measured using a point-of-care machine. Venous blood (approximately 5mL) was withdrawn via a needle and syringe from the patient and placed into a vacutainer tube. Serum was removed from the vacutainers using a pipette, 0.1ml was placed onto the Triage BNP cartridge, then into the Triage BNP<sup>®</sup> analysis machine (Biosite Diagnostics, Inverness Medical Innovations). This method of determining BNP levels has been demonstrated to provide reproducible, accurate and valid results.<sup>115</sup>

### Sociodemographic and clinical characteristics

In order to characterize patients, they were interviewed and answered questionnaires to obtain the following information: age, gender, marital status, smoking history, exercise patterns, comorbid conditions, NYHA classification, lifestyle behaviors and current medications, including vitamins, over the counter drugs or herbal supplements. The research nurse collected information on comorbid conditions using the interview format of the Charlson Comorbidity Index (CCI)<sup>116, 117</sup>. This index was developed to classify comorbid conditions that might change the risk of mortality. The index predicts short-term and long-term mortality in several situations including patients with heart disease including HF, cancer, stroke, renal disease, and frail elders<sup>97, 117</sup>.

#### Dietary intake assessment

Dietary nutrient intake of sodium and lycopene was assessed using a 24-hour diet recall method to determine (1) natural intake of lycopene in order to describe the lycopene intake in food products consumed in the control and intervention groups, and (2) sodium intake, as lycopene containing foods that are processed often contain higher levels of sodium. A 24 hour diet recall was collected at the baseline data collection visit and then randomly once a week for 3 weeks for a total of 4 recalls for each patient. The research nurse provided each patient with detailed instructions on how the diet recall information would be obtained. The information provided during the 24-hour recall was recorded onto a secure laptop and then entered into a computer software program titled Nutrition Data System (NDS) software (NCC, University of Minnesota)<sup>118</sup>. This program was used to analyze the nutrient content of the dietary recall. The NDS software provides output for 126 nutrient and nutrient ratios from the food intake data. The database, which is updated twice yearly, contains ingredient information for over 19,000

foods including over 8000 brand name and many ethnic foods<sup>118</sup>. There are data for over 160,000 food variants differing in preparation method or ingredients. The research nurse collecting data completed a certification process as a nutrition interviewer using the NDSR software.

### Research Procedures

The Institutional Review Board at the University of Kentucky granted permission to conduct this study. All patients gave informed written consent. A research nurse performed all procedures. The research nurse was an experienced cardiovascular advanced practice nurse who has completed certified training on protection of human subjects in research. During the first interview with the patients, the research nurse obtained sociodemographic and clinical data. Data about medications and supplements was obtained from the patient and verified through a review of the medical record. The research nurse also determined patients' New York Heart Association (NYHA) functional class by interviewing patients and determining their ability to perform their usual activities and the occurrence of any symptoms with those activities. The patient interview and questionnaires were completed at the baseline visit and again at the post-intervention visit one month later. The visits took place at a prearranged time such as before or after a cardiology clinic visit, cardiac rehabilitation session, in their home or at a place of convenience the participant chose.

Patients were randomized to one of two groups following completion of baseline data collection. A computer generated random number/block chart was utilized. Patients in both groups were given detailed instructions regarding 24-hour dietary recall. Serving size

estimation charts were provided to patients to assist with accuracy in conducting diet recalls.

The dietary recalls took between 15-20 minutes to complete.

### Intervention

Patients randomized to the intervention group received a month's supply of V8® 100% Low-Sodium Vegetable juice (30 cans). Patients were asked to consume one can each day. They were instructed that the entire can of juice could be consumed at one time or at separate times as long as the entire can was consumed each day. Patients were also asked to keep track of how many total cans they consumed during the month; this was to facilitate fidelity to the intervention. V8® is vegetable juice, which is tomato based. Each 11.5 ounces of V8® juice contains the following: 24 mg of lycopene; 70 calories; 140 mg of sodium; vitamins A and C; 820 mg of potassium; 2% of the recommended daily allowance for iron and magnesium; and 3 grams of fiber. This product contains a variety of vegetables (i.e., tomatoes, carrots, celery, beets, parsley, lettuce, watercress, and spinach)<sup>119</sup>.

### Statistical Analysis

The research nurse reviewed all questionnaires for completeness and legibility while the patients were still present. All data analyses were conducted using SPSS version 17.0 and a *P* value of < .05 was considered statistically significant. Descriptive analyses are presented as frequencies and means ± standard deviations as appropriate to the level of measurement of the variables. To compare baseline differences in sociodemographic and clinical characteristics between the two treatment groups, t-tests or chi-square were used. Intention to treat principles were applied to all data analysis. First, repeated measures ANCOVA was used to assess whether the changes over time in the outcome measures differed between the



intervention and control groups, controlling for BNP level. Then, multifactorial repeated measures ANCOVA was used to evaluate whether gender or BNP interacted with group to produce a differential impact on CRP and uric acid levels.

## **Results**

### Patient Characteristics

Characteristics of the total group and of the groups compared are displayed in Table 1. A total of 40 patients who were all categorized as NYHA class II or III were enrolled. Most patients had an ischemic HF etiology. There were no significant differences between patients in the control group or the intervention group with respect to age, gender, body mass index, HF etiology, NYHA classification, medications prescribed, smoking history or exercise patterns (Table 3-1). All patients who enrolled in the study completed the study. There was only one side effect reported in relation to drinking V8 juice daily and that was an increase in bowel movements.

### Specific Aim 1

Repeated measures ANCOVA revealed that the intervention and control groups were similar on baseline measures of uric acid and CRP (Table 4-2). There were no differences at baseline or across time in the covariate, BNP, between or within the groups. There was no impact of the intervention on uric acid or CRP levels and there were no changes across time in the control group in uric acid level or CRP (Table 4-2).

Multifactorial repeated measures ANCOVA revealed that there was a gender by group by time effect on CRP ( $p = 0.024$  for the interaction; Figure 1), but not uric acid ( $p > 0.05$  for interaction and main effects; Figure 4-2) levels. There was no effect of the covariate, BNP level. Among women in the intervention group there was a significant decrease in plasma CRP levels at the post-intervention time point. There was no change in CRP levels among men in the intervention group, but there was a decrease across time in the control group (Figure 4-1).

In order to explore potential reasons for the gender difference in the impact of the intervention, we compared men and women on baseline BMI and CRP levels. There were no differences between women and men in BMI ( $31.9 \pm 9.7$  vs  $30.7 \pm 6.7$ , respectively;  $p = 0.638$ ). There were difference in CRP levels between women and men ( $5.69 \pm 3.5$  vs  $2.86 \pm 2.62$ , respectively;  $p = 0.01$ ).

### Specific Aim 2

Plasma lycopene levels significantly increased in the intervention group after daily consumption of V8® 100% vegetable juice for 30 days, while there was no change in the control group (See Figure 4-2;  $p = 0.02$ ). There was no interaction of gender and group with regard to the effect of the intervention on lycopene levels ( $p = 0.37$ ). Plasma lycopene levels increased in both men and women over time in the intervention group, but not in the control group.

### Specific Aim 3

There was no significant group by time interaction on sodium intake (See Table 3;  $p = 0.237$ ). There was no main effect of either time or group on sodium intake (Table 3,  $p = 0.153$ ).

## Discussion

This is the first study in which a dietary lycopene intervention has been tested in a sample of patients with HF. To date, there have been only two other studies in which the role of dietary lycopene in patients with HF was assessed. In both studies, there was a positive association between plasma lycopene levels, oxidative stress and HF<sup>77, 78</sup>, but both of these studies were observational. In order to come to any firm conclusions about the effect of lycopene in patients with HF, randomized, controlled studies are needed.

In our randomized, controlled study, we did not see an impact of the intervention on either CRP or uric acid levels in the total group. We did, however, see a differential effect of gender in the effect of the intervention on CRP levels, but not uric acid. In women, the intervention resulted in a significant decrease in CRP across time, but not in men.

There are three major potential explanations for our finding of a gender effect in the intervention. The possibilities include (1) greater adherence to the intervention in women than in men, (2) the effect of BMI and adiposity, and (3) the higher CRP levels seen in women. With regard to the first potential explanation, there is published evidence that women are more adherent to prescribed HF regimens than men.<sup>120</sup> There was, however, no evidence in our sample that women were more adherent than men. Lycopene levels increased significantly in both men and women in the intervention group over time, while remaining unchanged in the control group.

With regard to the second potential explanation for our findings, increased BMI and adiposity found in women may be plausible reasons. The adipose tissue produces inflammatory cytokines such as interleukin-6 and tumor necrosis factor-alpha, which contribute to

atherosclerosis. IL-6 enhances liver production of CRP. Levels of inflammatory markers in obese persons ( $\text{BMI} \geq 30 \text{ kg/m}^2$ ) are considered independent predictors of CVD. Lycopene increases in adipose tissue and may exert its action on inflammatory cytokines. Abdominal adiposity has been associated with risk of CHD in women<sup>121, 122</sup>. Higher waist-hip-ratio (WHR) and greater waist circumference have been found to be independently associated with a significantly increased age-adjusted risk of CVD and HF.<sup>121, 123, 124</sup> In the Nurses' Health Study, women with a WHR of 0.88 or higher had a relative risk (RR) of 3.25 (95% confidence interval, 1.78-5.95) for CVD compared with women with a WHR of less than 0.72.<sup>121</sup> There was no gender difference in BMI level in our sample of patients. However, we did not have a measure of abdominal adiposity, most commonly measured by waist circumference or WHR. This additional measurement may have shed additional light onto our findings.

With regard to the third potential explanation for our findings, women have higher levels of CRP than do men.<sup>125</sup> For example, women participants enrolled in the Women's Health Study had a median CRP level of 0.42mg/dL compared with 0.28mg/dL in men.<sup>126</sup> In our sample, women had significantly higher baseline CRP levels than men. Often, the effect of a variety of interventions (e.g., cardiac rehabilitation, weight loss, intake of healthy foods) is greater in those in whom the outcome of interest is most negatively affected. That is, those who have the most to gain (or lose), often show the largest effects of an intervention, at least initially.<sup>127-132</sup> Thus, it is plausible that the substantially higher levels of CRP seen in the women in our study allowed the intervention to better exert its effects.

There is sufficient evidence to support that CRP plays a direct role in inflammation.<sup>133</sup> The fact that our study found CRP levels decreased in response to a dietary intervention is a

positive finding. Any decrease in CRP levels, such as the one observed in our study, has the ability to reduce the risk of further cardiac events and is considered to be of important value to clinicians and patients.<sup>125, 134</sup> A CRP in the highest quartile >0.73mg/dL had a five times greater risk of developing an acute myocardial infarction or stroke compared to those in the lowest quartile.<sup>126</sup> CRP levels have also been shown to predict mortality in patients with dilated cardiomyopathy and to have an inverse association with left ventricular function in patients with HF.<sup>135 136</sup> If CRP levels have increased in patients affected by HF, they will further increase with the severity of the pathology and be associated with a higher rate of mortality independently of any ischemic cause.<sup>46, 136</sup>

Our data also indicate that increased consumption of lycopene containing food products results in increased plasma levels of lycopene. These data support other findings that increased dietary intake of lycopene is reflected in plasma samples, indicating the bioavailability of lycopene in human plasma<sup>57, 60, 137</sup>. Adherence to the lycopene intervention was observed in both women and men in our sample.

Uric acid levels did not change as a result of the intervention, suggesting serum uric acid may not be a robust indicator of oxidative stress in patients with HF. High serum uric acid levels have been identified as a strong, independent marker of impaired prognosis in patients with moderate to severe CHF<sup>138</sup>. Uric acid excretion depends on renal function and may be compromised by diuretic treatment in these patients. The increased accumulation of reactive oxygen species (ROS) as a by-product of xanthine oxidase activity, is thought to be one of the underlying pathologic characteristics of increased uric acid in HF<sup>139</sup>. Inflammatory immune activation and increased ROS accumulation (See Figure 4-Pathway of Inflammation and

Oxidative Stress”), along with up-regulation of xanthine oxidase activity may contribute to oxidative stress found in the setting of HF<sup>140 141</sup>. However, our study did not find serum uric acid to be robust indicator of oxidative stress in a sample of patients with HF. This may be a result of the small sample size or that uric acid production occurs upstream in the pathway of oxidation and inflammation (See Figure 4).

Processed foods containing high levels of lycopene also contain high levels of sodium. Approximately 80% of the sodium in the average American diet comes from processed foods. Dietary sodium indiscretion is considered to be a precipitant in >20% of patients hospitalized for decompensated HF and high sodium intake is an independent risk factor for HF exacerbation.<sup>104-106</sup> Data from an earlier investigation suggest that foods containing high levels of lycopene may be beneficial regardless of their sodium content<sup>142</sup> The findings in the current study did not indicate an increase in sodium intake between the two treatment groups. However, even if a small increase in sodium levels had occurred, the benefit of the strong antioxidant lycopene used in the intervention may not have had a negative impact on patients with heart failure.

An important challenge in translating these findings into clinical treatment strategies relates to the fact that most clinical studies have been designed on top of established pharmacological therapy, whereas most experimental studies test novel interventions without concomitant drug regimens such as ACE inhibitors or beta-blockers. However, our study tested a randomized intervention on top of evidence-based drug regimens for patients with HF and

still found an impact of a dietary intervention. This is exciting and demonstrated a fruitful area of additional research related to dietary lycopene interventions.

With regards to the feasibility of this randomized, controlled trial of a dietary intervention with lycopene, we found patients with HF were able to adhere to the intervention as evidenced by a compliance rate of 100%. We also found this was an easy and inexpensive intervention to implement. The V8® juice cost less than \$1.00 per serving and is found in most urban and rural grocery stores. The patients did not report any ill effects from drinking the lycopene product for 30 days and only one person reported a mild side effect of increased bowel movements. This intervention was a simple and easily implemented dietary intervention and was well accepted and followed by a sample of patients with difficult self-management regimens.

### Limitations

Limitations exist when investigating the impact of a single micronutrient in a complex condition such as HF. First, this investigation was conducted in a small sample of patients with HF. A larger sample size may assist in understanding mechanistic pathways for the interaction we observed. A larger sample also needs to be studied in order to confirm the presence of a gender interaction with the intervention. Secondly, the biological measurements that were obtained in this study were collected at only two different time points and may not be reflective of overall inflammatory status or oxidative stress in patients with HF.

## Conclusion

The study of the role of dietary or whole food sources of micronutrients as interventions for inflammation and oxidative status in patients with HF is novel. To date, investigators have largely studied supplements as sources of micronutrients. Lycopene is a natural plant compound found in fruits and vegetables. Lycopene-containing products are inexpensive, readily available, shelf-stable, and versatile. In a sample of patients with HF who received a dietary lycopene intervention, we found a significant increase in plasma lycopene levels. Serum CRP levels, as a biomarker of inflammation, significantly increased in the intervention group but within females only. These findings suggest the naturally occurring antioxidant lycopene interacts with gender to affect CRP levels in a sample of patients with HF. Although a physiologic mechanism is unclear, additional studies will help clarify this finding. This study provides insight to the potential role of lycopene in HF and may lead to additional treatment strategies. These findings are a preliminary step in a process of establishing efficacy of a specific dietary intervention with antioxidants that may have an effect on inflammation and oxidative stress in HF.



## Chapter Five

### Conclusions and Discussion

The enormous impact heart failure (HF) places on individuals and on our healthcare system continue to drive the search for cost-effective treatment strategies. HF affects nearly 6 million people in the United States alone and the number of new cases is expected to increase by more than 600 thousand cases each year.<sup>8,9</sup> Projected medical costs for the treatment of HF are expected to increase by approximately 200% by the year 2030.<sup>143</sup> Current treatment strategies include multiple drug regimens with the evidenced-based use of angiotensin-converting enzyme inhibitors (ACE), beta-blockers (BB), diuretics, and spironalactone.<sup>144</sup> Invasive procedures for the treatment of HF include placement of implantable cardio-defibrillators (ICD) and cardiac resynchronization therapy (CRT).<sup>144</sup> Both of these strategies account for the high costs related to treatment of HF. In addition to rising treatment costs, there is an increase in the number of patients with HF due to the overall aging of the population.<sup>143</sup> Cumulatively, these issues are the momentum for researchers to find novel therapeutic and economical interventions that are easily combined with current treatment strategies.

The overall goal of treatment for HF is to reduce the substantial symptom burden that accompanies HF. HF is a condition of chronic exacerbations of volume overload and myocardial injury resulting from an intricate relationship between biochemical and biological mechanisms. Recent research has provided evidence that inflammation and oxidative stress contribute to the development and progression of HF.<sup>40, 145</sup>

Inflammation and oxidative stress, independently and mutually, can reduce myocardial contractility leading to a reduction in cardiac index. At the cellular level, inflammation increases endothelial dysfunction via an inflammatory pathway activated by direct antigenic stimulation or cytokine release in response to hemodynamic stress.<sup>42, 48, 50</sup> Inflammatory cytokines, once thought to be produced solely by the immune system, are now known to be synthesized by the cardiomyocyte and can stimulate myocardial dysfunction by remodeling of the myocardium interstitium through myocyte hypertrophy, apoptosis, and endothelial damage.<sup>146, 147</sup>

Oxidative stress is the outcome when there is an imbalance between the reactive oxygen species (ROS) production and the antioxidant defense mechanisms in the body.<sup>112, 148, 149</sup> Oxidative injury occurs when the system is overwhelmed by free radicals and modification occurs to organic molecules.<sup>112, 150, 151</sup> Antioxidants provide protection by scavenging and detoxifying the free radicals, thus maintaining a homeostatic balance at the cellular level.<sup>47, 152</sup>

Antioxidant nutrients may slow the progression of HF because of their ability to inhibit damaging oxidative and inflammatory processes. Chapter two of this dissertation was a review of the current research literature related to antioxidants and heart failure. Specifically, I reviewed the literature to identify any investigations with the antioxidant lycopene used as a dietary intervention with HF patients. As a result of this review, I found that there were no intervention studies using lycopene in patients with HF, but that there to be strong evidence to support the role of antioxidants in cardiovascular disease.<sup>69, 71-73, 113</sup> I also found strong evidence supporting the role of inflammation and oxidative stress for improving outcomes in patients with HF<sup>40, 50, 112, 145, 150, 153, 154</sup>. Several studies have been conducted with lycopene and other antioxidants in healthy individuals and an inverse relationship has been observed between

increased lycopene intake and cardiovascular disease risk.<sup>59, 60, 62, 63, 67, 89, 101, 155-158</sup> To date there have been two case-control studies in which lycopene was investigated as the variable of interest in a sample of HF patients.<sup>77, 78</sup> Significantly higher levels of oxidative stress and lower levels of plasma antioxidants were found in HF patients in comparison to controls. Among HF patients, and ejection fraction (indicating disease severity) was found to be inversely correlated to isoprotane levels (biomarker of oxidative status) and directly correlated to plasma levels of dietary lycopene.<sup>77, 78</sup> Collectively, these data provide evidence for the potential role of dietary antioxidants in reducing inflammation and oxidative stress, thus potentially reducing symptom burden in patients with HF.

Chapter three of this dissertation is a longitudinal prospective study in which levels of dietary lycopene and sodium intake were measured. Rehospitalizations and cardiac mortality data were obtained to examine the relationship between dietary lycopene intake and cardiac event-free survival after stratifying patients by sodium intake levels. Dietary intake was measured by four-day food diaries. Food diaries were analyzed using the Nutrition Data System for Research (NDSR; Nutrition Coordinating Center, Minneapolis, MN).<sup>95</sup> Patients were grouped by the median split of lycopene level of 2471 mcg/day and stratified by daily sodium intake levels above and below 3 grams. Patients were followed for up to three years to collect data on HF hospitalization and cardiac mortality for event-free survival analysis. Cox proportional hazard regression was used to compare differences in cardiac event-free survival between higher and lower lycopene intake groups within each stratum of sodium intake level. Lycopene intake above 2471 mcg/day was associated with longer cardiac event-free survival compared with lower lycopene intake after controlling for age, gender, HF etiology, body mass index,

NYHA functional class, LVEF, and total comorbidity score ( $p = .003$ ). The worst cardiac event-free survival was observed in the low lycopene intake group regardless of sodium intake level ( $> 3$  grams  $HR = 3.01$ ;  $p = .027$  and  $\leq 3$  grams  $HR = 3.34$ ;  $p = .023$ ). These data suggest an increased dietary lycopene intake has the potential to improve cardiac event-free survival in patients with HF independent of sodium intake, thus lending support to the role antioxidants may have in patients with HF.

An intervention study was designed to test the impact of dietary lycopene on biomarkers of inflammation and oxidative stress specifically in patients with HF. This study is addressed in Chapter Four of this dissertation and was supported by the consistent protective effect of lycopene found in epidemiological, tissue and experimental studies.

A randomized-control feasibility trial was conducted with a sample of 40 HF patients assigned patients to one of two groups. The lycopene intervention group received 24 mg of lycopene intake per day by drinking an 11.5 ounce serving of V8 100% vegetable juice daily for 30 days. Group 2 (usual care) continued their usual diet. Four randomized phone calls were used to collect 24 hour diet recalls from the patients. We obtained serum lycopene, uric acid (biomarker of oxidative stress), C-reactive protein (biomarker of inflammation), and b-type natriuretic peptide (biomarker of HF disease severity) to determine the impact of the lycopene dietary intervention.

In this study we used repeated measures ANCOVA to assess whether the changes over time in the outcome measures differed between the intervention and control groups, controlling for BNP level. Then, multifactorial repeated measures ANCOVA was used to evaluate whether gender or BNP interacted with group to produce a differential impact on CRP and uric

acid levels. We also used repeated measures ANOVA to test the impact of the intervention by gender. The results of this investigation found plasma lycopene levels increased insignificantly in the intervention group compared to the control group respectively (.51mmol/L to .76mmol/L,  $p = .002$ ; .56mmol/L to .58mmol/L. There was also a significant interaction between CRP group and gender in the impact of the intervention on CRP levels; CRP levels decreased significantly in the intervention group in women and but not in men, ( $p = .024$ ). Uric acid and BNP did not demonstrate a change related to the intervention as hypothesized in this study. These findings suggest the naturally occurring antioxidant lycopene interacts with gender to affect inflammation, as measured by CRP, in an intervention of increase dietary lycopene in a sample of patients with HF.

The feasibility study and the longitudinal study combined are the beginning of a program of research specifically focusing on the potential role of dietary lycopene in reducing inflammation and oxidative stress in patients with HF. The potential impact of a dietary intervention to reduce symptom burden in HF is of great interest to clinicians and researchers as it poses a novel, innovative treatment strategy. A dietary intervention with a food product high in lycopene, such as V8 juice once a day, is an economical and easily combined treatment strategy with, very limited, if any side effects for patients with HF.

Additional studies are needed to further identify physiologic mechanisms of lycopene and to identify appropriate biomarkers to measure oxidative stress and inflammation in chronic HF as these remain unclear. Larger samples of patients with HF should be studied to validate the findings from the feasibility study. Antioxidants other than lycopene may be responsible for the impact of the intervention, or it may be a combination of antioxidants found in V8 juice. A

thorough examination of specific antioxidants and combined antioxidants should be conducted in similar studies.

Table 1-1: Definition of Terms- obtained from Taber's Cyclopedic Medical Dictionary,  
Nineteenth Edition

antioxidant- a agent that prevents or inhibits oxidation. A substance that may protect cells from the damaging effects of oxygen radicals, highly reactive chemicals that play a part in atherosclerosis, some forms of cancer, and reperfusion injuries.

bioactive- affecting living tissues

biochemical- of or related to biochemistry, the chemistry of living things, the science of chemical changes accompanying the vital functions of plants and animals

carotenoid- one of a group of more than 500 yellow, orange, or red fat soluble pigments found naturally in fruits and vegetables and acting as antioxidants in the body

endogenous- produced or originating from within a cell or organism

inflammation- an immunological defense against injury, infection or allergy, marked by increases in regional blood flow, immigration of white blood cells, and release of chemical toxins

micronutrient- any of the chemical elements required in minute quantities for growth of an organism

nutrient- a nutritious ingredient or substance in food

nutrition- the series of processes by which an organism takes in and assimilates food for promoting growth and replacing worn or injured tissues

oxidation- any process in which oxygen combines with an element or substance

peroxidase- any oxio reductase enzyme that acts as a catalyst in reactions in which a peroxide is reduced

peroxide- any oxide containing the O<sub>2</sub> group in which the two atoms of oxygen are linked by a single bond

phytochemical - chemical processes associated with plant life, and the chemical compounds produced by plants

reactive oxygen species- a phrase used to describe a variety of molecules and free radicals (chemical species with one unpaired electron) derived from molecular oxygen. Molecular oxygen in the ground state is a bi-radical, containing two unpaired electrons in the outer shell (also known as a triplet state). If one of the two unpaired electrons is excited and changes its spin, the resulting species (known as singlet oxygen) becomes a powerful oxidant as the two electrons with opposing spins can quickly react with other pairs of electrons, especially double bonds.

scavenger - anything that removes impurities or refuse



Table 2-1: Dietary intervention studies with Lycopene in healthy Individuals

Study Author	Subjects	Type and duration of intervention	Results
Agarwal et. al, 2001 <sup>57</sup>	20 healthy individuals 10 male 10 female	Randomized crossover design Placebo= 0 mg lycopene Tomato juice = 50mg lycopene (500 ml) Spaghetti sauce = 40 mg lycopene (126 g)	1) Daily intake of spaghetti sauce or juice significantly increased serum levels of lycopene. 2) the avg. increase of any dietary treatment over placebo was 2-fold 3) dietary lycopene significantly lowered lipid oxidation measures (TBARS)
Bose & Agarwal, 2007 <sup>62</sup>	50 healthy & 30 CHD Selected to intervention	200 g cooked tomatoes = 25mg of lycopene 60 days	1) Significant improvement in serum levels of enzymes involved in antioxidant activity 2) Decreased lipid peroxidation rates 3) No significant changes in lipid profiles
Hadley, et.al 2003 <sup>60</sup>	60 healthy Randomized to intervention	1) Campbell's condensed soup = 35mg lycopene 2) Campbell's ready to serve soup= 23mg lycopene 3) V8 juice = 25mg lycopene 15 days	1) Increased protection of lipoproteins to oxidative stress 2) Lycopene isomers change rapidly with variation in dietary intake
Jacob, et.al 2008 <sup>63</sup>	24 healthy Randomized to intervention	1) 250 ml tomato juice with 90mg of Vit C twice daily 2) 250 ml of tomato juice with 870mg Vit C twice daily- 14 days	1) Reduction in serum total cholesterol levels and CRP with tomato juice consumption in both groups 2) Cholesterol reduction correlated with lycopene uptake
Bub, et.al 2000 <sup>64</sup>	23 non-smoking men	Feeding study 1) 2 week intake of low carotenoid content 2) 2 week intake of 330 ml tomato juice=40mg lycopene 3) 2 week intake of 330ml carrot juice= 15.7mg $\alpha$ -carotene & 22.3mg $\beta$ -carotene 4) 2 week spinach powder = 11.3mg of lutein and 3.1mg $\beta$ -carotene 8 weeks	1) Tomato juice consumption increased TBARS by 12% and increased lag time for lipoprotein oxidation- reducing LDL oxidation 2) Carrot juice and spinach powder had no effect on lipid peroxidation
Frohlich, et.al 2005 <sup>61</sup>	17 non-smoking volunteers Randomized to intervention	1) 145-320 g tomatoes/day = 12.5mg lycopene 2) 94-101 g tomato juice/day = 12.5mg lycopene 3) 25-28 g tomato puree/day = 12.5mg lycopene 4 weeks	1) Following intervention, plasma lycopene increased significantly 2) Supplementation did not affect levels of tocopherols and ascorbic acid in plasma 3) Lycopene isomerization changes within the body after ingestion
Unlu, et.al 2005 <sup>61</sup>	11 healthy non-smoking subjects	Feeding study 1) 300g Salsa w/avocado and w/o avocado & 3 slices of fat free bread 2) 220g Salad with carrots, lettuce, baby spinach & 40g fat free Italian salad dressing with 2 slices of fat-free bread-8 weeks	1) Lycopene and $\beta$ - carotene absorption from salsa with avocado was significantly higher than the control meal
Van het Hof et.al 2000 <sup>65</sup>	33 volunteers, divided into 2 groups by gender	Split plot design- heat treatment and homogenization A pasta meal served at lunch for 4 cons. days (no other fruits or vegetables were served on these days) served with macaroni, ham and a white sauce and a dessert of custard 1. canned tomatoes- 55 min of heat at 100 degrees Celsius 2. canned tomatoes- blended, homogenized and heated 3. canned tomatoes- minimally heated at 80 C	1) Additional heat and homogenization enhanced the release of lycopene; additional heating was not always significant.  2) short term increased lycopene intake is a good model to compare the bioavailability from different food sources

Table 2-2: Literature Search

<b>Search Terms</b>	PubMed	CINAHL	Cochrane
<i>Lycopene</i>	2682	406	4
<i>Lycopene &amp; HF</i>	3	2	0
<i>Lycopene &amp; oxidative stress</i>	304	42	1
<i>Lycopene &amp; inflammation</i>	76	14	8
<i>Lycopene &amp; heart disease</i>	104	10	7
<i>HF &amp; antioxidants</i>	2371	55	1

Table 3-1: Patient characteristics N = 212

Characteristics		(%) or Mean $\pm$ SD		
		Total	Lycopene $\leq$	Lycopene $>$
		(n = 212)	2471 mcg/day	2471 mcg/day
Age (years)		60 $\pm$ 12	59 $\pm$ 12	61 $\pm$ 13
Gender	Male	143 (67.5)	66 (62.3)	77 (72.6)
	Female	69 (32.5)	40 (37.7)	29 (27.4)
Body mass index (kg/m <sup>2</sup> )		30.5 $\pm$ 7.6	30.5 $\pm$ 7.4	30.4 $\pm$ 7.8
Normal weight (< 25.0)		49 (23.1)	24 (22.6)	25 (23.6)
Overweight (25.0 to 29.9)		60 (28.3)	26 (24.5)	34 (32.1)
Obese ( $\geq$ 30.0)		103 (48.6)	56 (52.8)	47 (44.3)
NYHA functional class	I	15 ( 7.1)	4 ( 3.8)	11 (10.4)
	II	81 (38.2)	40 (37.7)	41 (38.7)
	III	87 (41.0)	48 (45.3)	39 (36.8)
	IV	29 (13.7)	14 (13.2)	15 (14.2)
Heart failure etiology	Non-ischemic heart disease	122 (57.5)	64 (60.4)	58 (54.7)
	Ischemic heart disease	90 (42.5)	42 (39.6)	48 (45.3)
Medication	ACE inhibitors	143 (67.5)	71 (67.0)	72 (67.9)
	ARB II*	39 (18.4)	14 (13.5)	25 (23.8)
	Digoxin	62 (29.2)	30 (28.8)	32 (30.2)

β blocker	185 (87.3)	95 (89.6)	90 (84.9)
Diuretics	163 (76.9)	78 (74.3)	85 (81.0)
Aldosterone antagonist	45 (21.2)	25 (23.8)	20 (18.9)
Left ventricular ejection fraction (%)	33.9 ± 14.0	34.0 ± 14.9	33.8 ± 13.2
< 40%	136 (64.2)	66 (62.3)	70 (66.0)
Total comorbidity score	3.0 ± 2.0	3.0 ± 1.9	3.0 ± 2.1
Hypertension	147 (69.3)	77 (73.3)	70 (67.3)
Diabetes mellitus	80 (37.7)	41 (38.7)	39 (36.8)
Sodium (mg/day)*	3256 ± 1193	3029 ± 1087	3483 ± 1254
Less than 3,000 mg/day	109 (51.4)	60 (56.6)	49 (46.2)
Greater than 3,000 mg/day	103 (48.6)	46 (43.4)	57 (53.8)

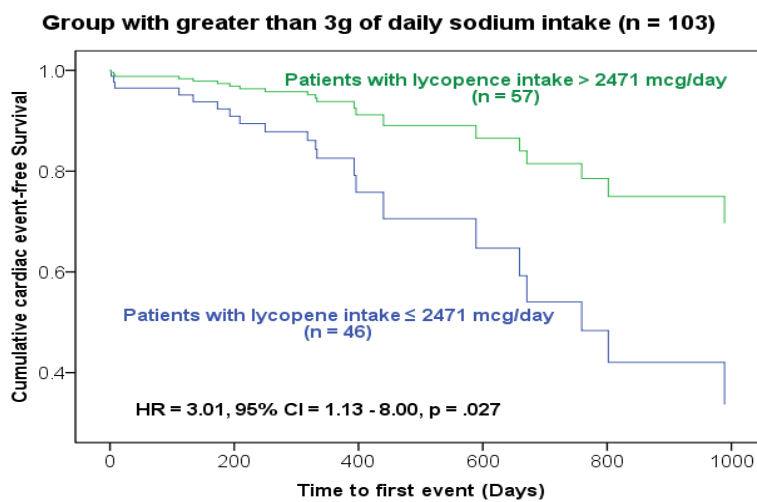
**Figure Legend:** ACE= angiotensin converting enzyme; ARB II= Angiotension II receptor blocker;

NYHA= New York Heart Association; \* p < 0.05 in the independent t-test

Figure 1A and 1B. Difference in time to event between 2 groups with higher and lower lycopene intake stratified by sodium intake

*Survival curves were adjusted for age, gender, HF etiology, BMI, LVEF, NYHA class, and total comorbidity score after stratifying by sodium intake.*

**Figure 1A**



**Figure 1B**

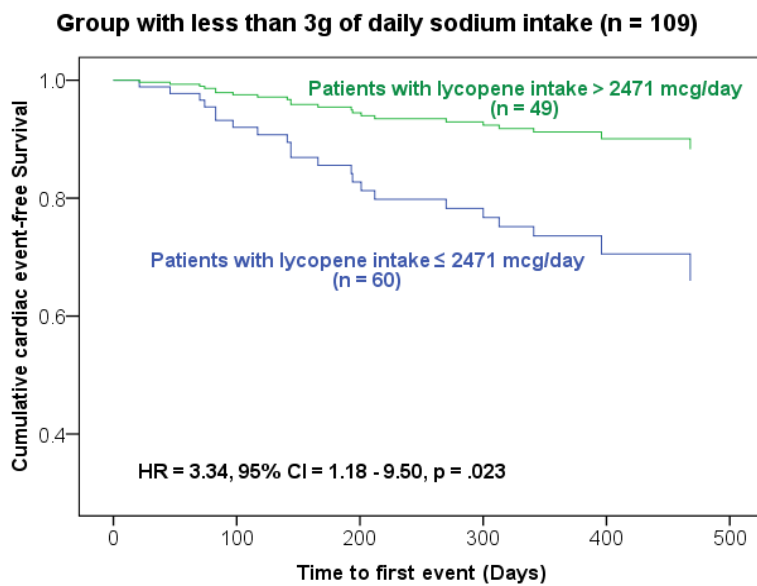


Table 4-1: Patient Characteristics

Characteristics		N (%) or Mean $\pm$ SD			
		Total	Intervention	Control	P value
		(n = 40)	(n= 22)	(n= 18)	
Age (years)		65 $\pm$ 9	65 $\pm$ 11	65 $\pm$ 9	.999
Gender	Male	23	8 (35)	15(65)	.131
	Female	17	10 (59)	7 (41)	
Body mass index (kg/m <sup>2</sup> )		31 $\pm$ 8	30 $\pm$ 5	32 $\pm$ 9	.257
NYHA class	II	28 (70)	16 (57)	12 (43)	.677
	III	12(30)	6 (50)	6 (50)	
Heart failure	Non-ischemic	6 (15)	5 (83)	1 (17)	.130
etiology	Ischemic	40 (85)	17(50)	17 (50)	
Medication	ACE inhibitors	35 (88)	16 (46)	19 (54)	.987
	$\beta$ blocker	30 (75)	17 (57)	13 (43)	
	Diuretics	19 (48)	9 (47)	10 (53)	
Smoking History	Current	8 (20)	4(50)	4(50)	.935
	Former	20 (50)	11(55)	9 (45)	
	Never	12/40 (30)	6 (50)	6 (50)	
Exercise frequency	< 1 hour/week	21/40 (53)	11(52)	10 (48)	.726
	$\geq$ 1 hour/ week	19/40 (47)	11 (58)	8 (42)	
BNP Levels, pg/ml	Baseline	167 $\pm$ 198	196 $\pm$ 237	132 $\pm$ 133	.316

Table 4-2: Serum C-reactive Protein and Uric Acid Pre- and Post-Intervention Compared  
Between the Groups Using B-type Natriuretic Peptide as a Covariate

	C-reactive Protein mg/L*		Uric Acid mg/dl*	
	Intervention	Control	Intervention	Control
Baseline	3.4 ± 3.1	4.8 ± 3.4	7.2 ± 1.5	7.2 ± 2.3
Post-Intervention	3.1 ± 2.8	4.5 ± 3.8	7.2 ± 1.3	7.3 ± 2.5

Legend: Post-intervention was 30 days after baseline; \*p > 0.05 for time and group effect

Table 4-3: Sodium and Lycopene Levels by Dietary Intake

	Sodium intake*			Lycopene intake		
	Total	Intervention	Control	Total*	Intervention	Control
Baseline	2671 ± 1252	2858 ±1389	2443 ± 1055	9310 ± 12849	10543 ± 14174	7802 ± 11235
Post- Intervention	2864 ± 1036	3182 ±1063	2474 ± 879	14775 ± 11926	23317 ± 8332	4336 ± 5545

Legend: Sodium = mg/day; Lycopene = mcg/day; Post-intervention was 30 days after baseline;

\*p > 0.05 for time and group effect



Figure 4-1: C-reactive Protein Levels Pre- and Post-Intervention Compared Between Groups by Gender

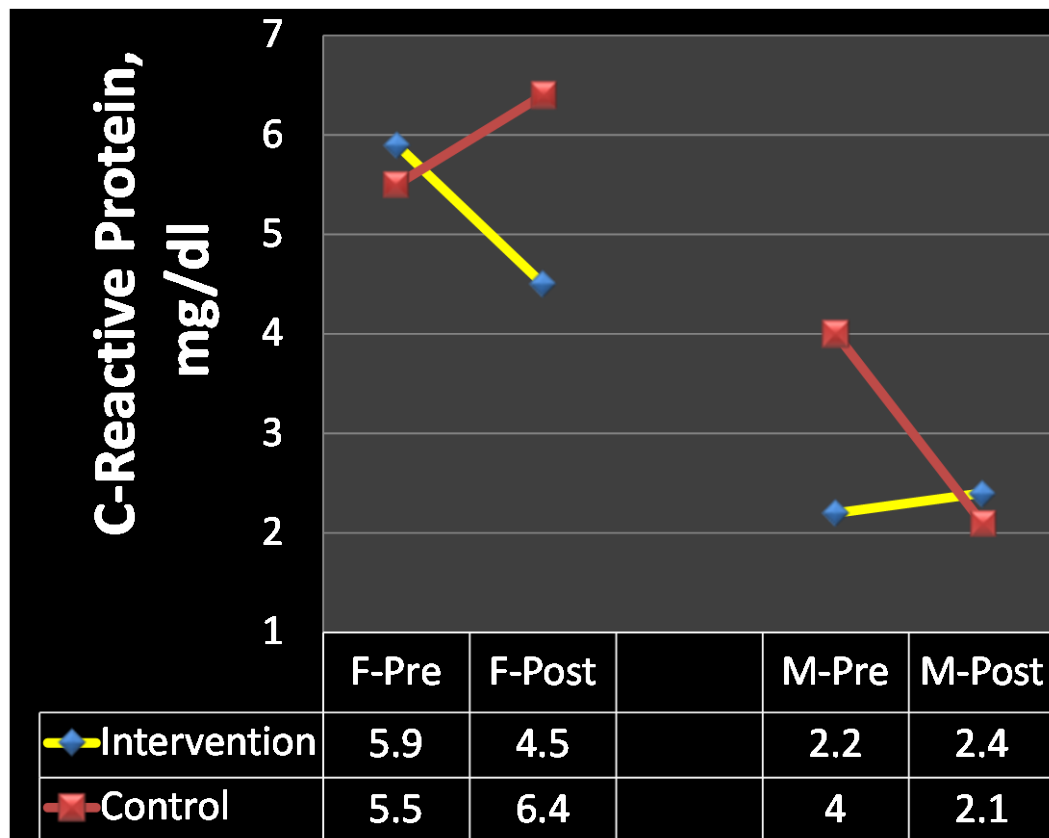


Figure Legend- F= Female; M= Male

Figure 4-2: Uric Acid Levels Pre- and Post-Intervention Compared Between Groups by Gender

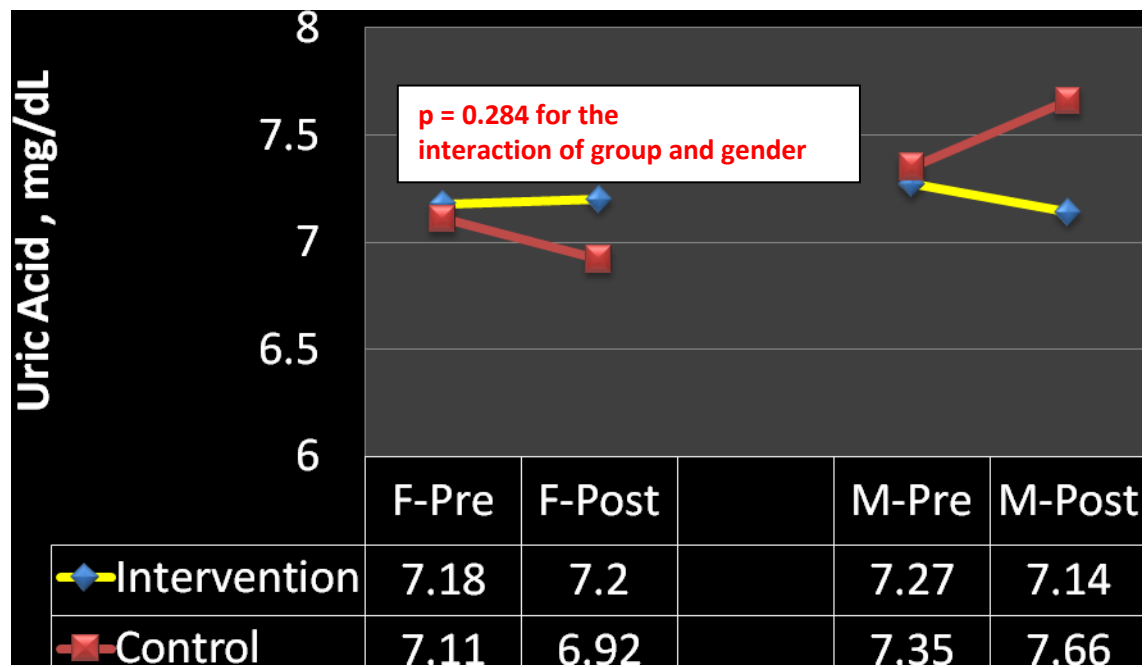


Figure Legend- F= Female; M= Male

Figure 4-3: Plasma Lycopene Compared Across Time Between the Groups

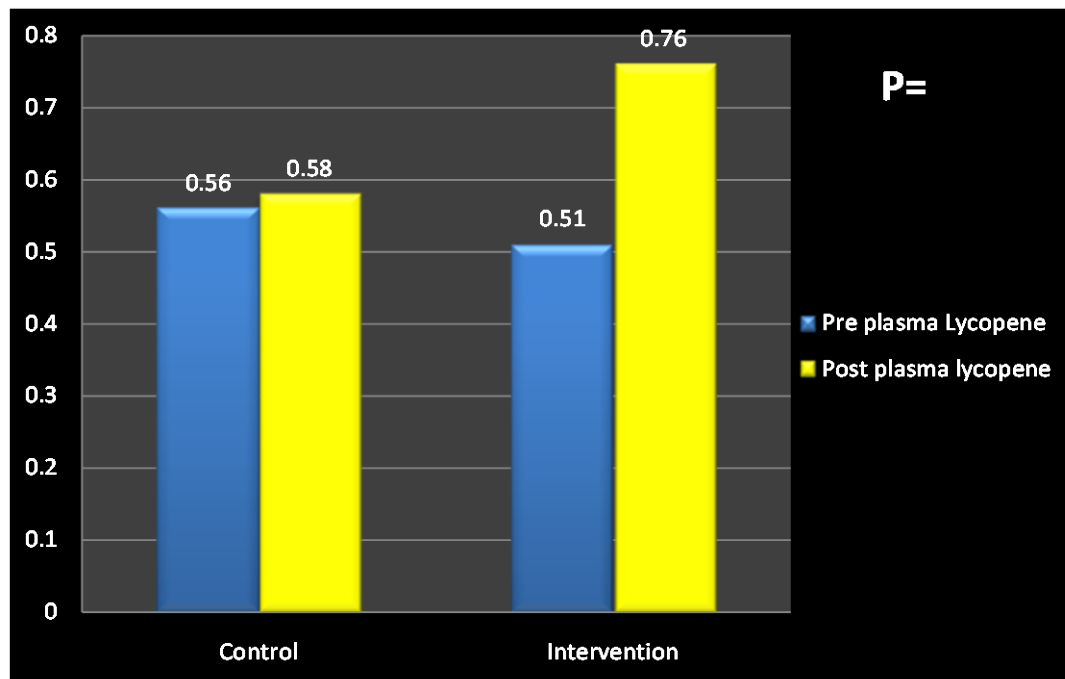
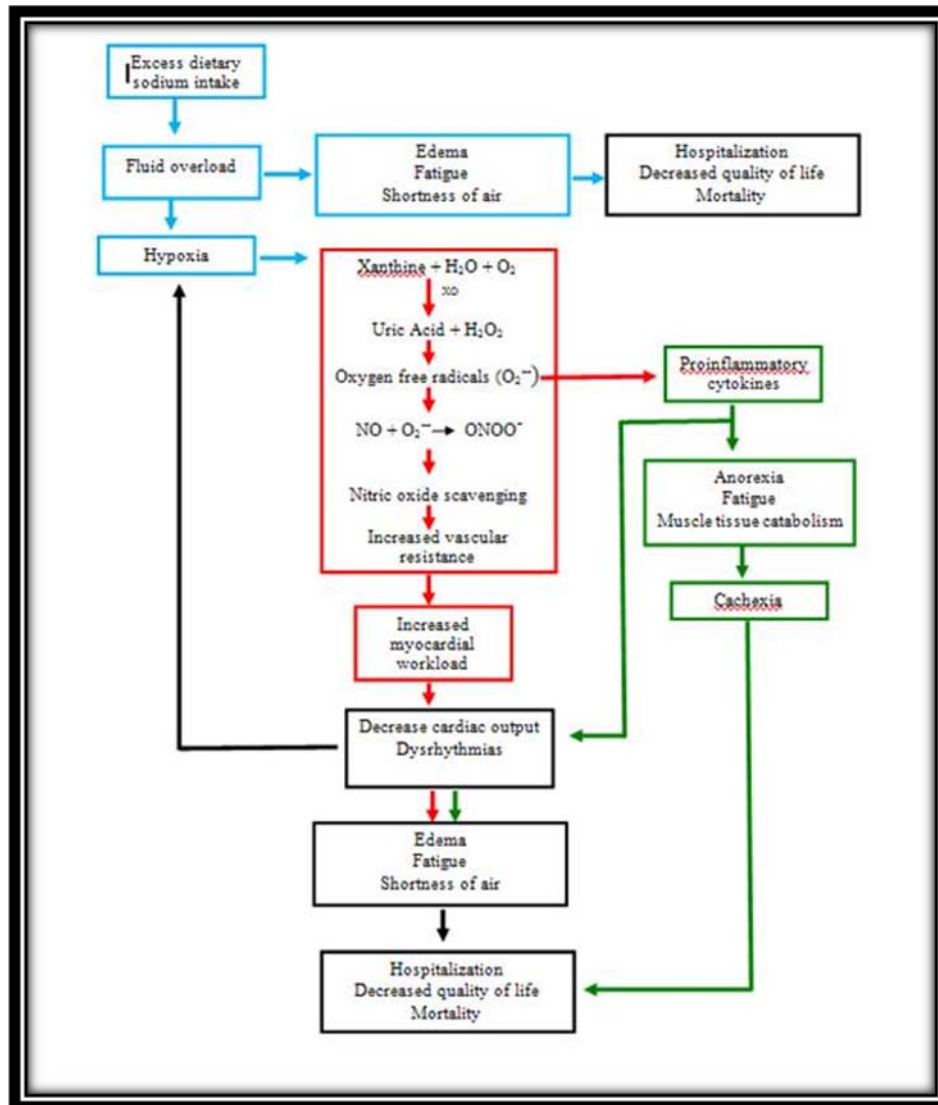


Figure Legend- Plasma lycopene = mmol/L; Pre = Baseline measurement; Post = after intervention for 30 days

Figure 4-4: Pathway of Inflammation and Oxidative Stress in Patients with Heart Failure



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Educational Institutions attended and degrees awarded

- a. University of Kentucky, 2002 MSN
- b. Thomas More College, 1987 BSN
- c. Northern Kentucky University, 1984 General Studies

Professional Positions Held

- a. University of Kentucky, Director of Operations, RICH Heart Program- College of Nursing
- b. Georgetown Community Hospital, Director of Cardiovascular Nursing
- c. University of Kentucky, Research Associate
- d. Midway College, Adjunct Clinical Instructor
- e. Georgetown Community Hospital, Department Manager
- f. Georgetown Community Hospital, Staff Nurse
- g. St. Elizabeth's Medical Center, Staff Nurse

Scholastic and Professional Honors

- American Heart Association Heart Disease and Stroke Student Scholarship Award, 5/2002
- Presidential Award, College of Nursing Alumni Association, 5/2002
- Nursing Research Award, 7<sup>th</sup> Annual Scientific Meeting of the HFSA, 9/2003. Presentation of the abstract: *Following a Sodium Restricted Diet: Attitude and Barriers"*
- Best Doctoral Student Podium Presentation, University of Kentucky, College of Nursing- Student Showcase 4/10/2009

Professional Publications

1. Biddle, MJ; Payne-Emerson, H; Heo, S; Song, E; Lennie, TA; Dunbar, S; Pressler, SJ; Kim, J; Moser, DK (2008). Lycopene Intake Predicts Event-Free Survival in Patients with Heart Failure. *Circulation*, 118 S920.

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